REMARKS

Claims 1-9, 11-18, 20-28, and 39-44 are pending. Claims 1, 20, and 24 have been amended and claim 10 has been canceled without prejudice or disclaimer. Claims 39-44 are new. Support for the amendments and new claims can be found in the application as filed, for example, in original claim 10 and at page 4, last par. No new matter has been added.

Examiner Interview

Applicants thank the Examiner for conducting a telephonic interview with Applicants' representative on July 31, 2009. During the interview, the obviousness rejection and proposed claim amendments were discussed.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the 35 U.S.C. § 102 rejection that was pending in the previous Office Action.

Withdrawn Objection

Applicants thank the Examiner for withdrawing the previously-raised objection to the claim identifiers.

35 U.S.C. § 103

Ladner and Anderson. The Office at pages 3-11 of the Action maintains its position that claims 1-9, 13, 15-17, and 20-27 are allegedly obvious in light of Ladner (U.S. Pat. No. 5,403,484; hereinafter "the '484 patent") and Anderson (U.S. Pat. No. 6,649,419; hereinafter "the '419 patent").

Ladner, Anderson, and Janda. At pages 11-12, the Office alleges that claims 1-10, 12-17, and 20-28 are obvious in light of the '484 patent, the '419 patent, and Janda (U.S. Pat. No. 5,571,681; hereinafter "the '681 patent").

Ladner, Anderson, and McCafferty. The Office at pages 12-14 alleges that claims 1-9, 13, 15-18, and 20-27 are obvious in light of the '484 patent, the '419 patent, and McCafferty (U.S. Pat. No. 5,969,108; hereinafter "the '108 patent").

Ladner, Anderson, Janda, and Steinbuchel. At pages 14-15 of the Action, the Office alleges that claims 1-17 and 20-28 are obvious in light of the '484 patent, the '419 patent, the '681 patent, and Steinbuchel (U.S. Pat. No. 6,022,729, hereinafter "the '729 patent").

Applicants' Reply.

Applicants respectfully disagree with the Office's positions. However, in the interest of expediting prosecution, Applicants have amended the claims. As indicated in the amendments presented herewith, the claims recite, in part:

- A method of selecting phage that encode a target binding protein from a plurality of display phage. The method includes the step of producing replicate phage from the infected cells in the presence of the target immobilized to the support, thereby forming replicate phage immobilized to the support via binding to the target, wherein the producing is completed in less than 4 hours (e.g., claim 1);

- A method of identifying members of a bacteriophage library that have a desired binding property. The method includes the step of amplifying members of a subset of bacteriophage members in less than 4 hours (e.g., claim 20); and

- A method of selecting a nucleic acid that encodes a binding protein from a library of display phage. The method includes the step of producing phage from the infected cells in the presence of the target, the produced phage being replicates of phage that bind to the target, wherein the producing is completed in less than 4 hours (e.g., claim 24).

The methods recite that the producing steps are completed in less than 4 hours, or that less than 4 hours elapses in the amplifying steps. The cited references, whether considered alone or in combination, fail to render such methods obvious.

Original claim 10 had recited that the producing step in claim 1 is completed in less than 4 hours. The Office appears to rely on the '681 patent as allegedly rendering this element obvious. For example, the Office alleges at pages 11-12 of the Office Action:

> Although Ladner provides certain general guidelines and conditions for reaction times involving the phage, Ladner does not explicitly teach reaction times of less than 4 hours for step (e) or steps (d) and (f), as in claims 10 and 12, or the cycles being less than 8 hours as in claim 28; nor does Anderson. Ladner also does not explicitly teach a change in the temperature upon the producing step as in claim 14; nor does Anderson.
>
> Janda generally teaches the use of covalent conjugates that are immobilized by attachment to a substrate through a solid phase and are easily separated from unconjugated elements of the combinatorial library by stringent washing. Janda generally teaches combinatorial libraries employing phagemid-display are particularly preferred since such phagemids include genetic material for identifying and amplifying conjugated catalysts. In describing the reactions for contact phage with the host cell, incubating the cell, and expressing the phage in the host cell, the processes can be carried out in less than four hours, such as the 15 minutes to infect the XLI-Blue™ cells, and the 2 hour culturing - note that the overnight cell selection with kanamycin is not required due to the beads being able to select the phage of interest an only captures progeny phage produced from the first round of

binding to the bead that produced in the host cell (col. 25, lines 37-50). As in claim 14, Janda teaches going from room temperature during infection to 37 degrees C during incubation (col. 25, lines 37-50).

With this reply, Applicants present the Declaration of Robert Charles Ladner, Ph.D. ("Declaration"). As detailed at item 5 therein:

5. I disagree with the Office's position. The element of producing or amplifying phage in less than 4 hours would not have been obvious in light of the '681 patent, the '484 patent, or the '419 patent (alone or in combination).

Janda. *The passage the Office points to in the '681 patent discloses:*

> Phage are removed and each well is then washed with TBS/Tween (50 mM Tris-HCl at pH 7.5, 150 mM NaCl, 0.5% Tween 20) for five minutes at room temperature. The plate is washed with distilled water, and noncovalently adherent phage are eluted by the addition of 50 ul of elution buffer (0.1M HCl, adjusted to pH 2.2 with solid glycine) to each well and incubation at room temperature for five minutes. Covalently bound phage are eluted in two separate 50 µl washes with 20 mM DTT at 25C. The resulting DTT-eluates from each of the six libraries are combined.
>
> Eluted phage are used to infect 2 ml of fresh (OD_{600} =1) E. coli XL1-Blue cells for 15 minutes at room temperature, after which 10 ml of SB containing 20 ug/ml carbenicillin and 10 ug/ml tetracycline is admixed. Aliquots of (20, 10, and 1/10 ul are removed for plating to determine the number of phage (packaged phagemids) that are eluted from the plate. The culture is shaken for 1 hour at 37C, after which it is added to 100 ml of SB containing 50 ug/ml carbenicillin and 10 ug/ml tetracycline and shaken for 1 hour. Helper phage VCSM13 (10^{12} pfu) are then added and the culture is shaken for an additional 2 hours. After this time, 70 ug/ml kanamycin is added and **the culture is incubated at 37C overnight**. Phage preparation and further panning/affinity selections are repeated as described above. (col. 25, lines 27-50; emphasis added)

As this passage makes clear, the phage-related methods of the '681 patent require that phage-infected XL1 cells be grown overnight. Further, even prior to the overnight incubation step, the cells are incubated for additional periods of time: the phage-infected XL1 cells are incubated for an hour, then the phage-infected XL1 cells are added to 100 ml of SB and incubated for another hour, then helper phage are added to the culture containing the phage-infected XL1 cells, and the helper-phage infected culture is incubated for two hours. Thus, in light of the '681 patent's disclosure, a skilled practitioner would incubate phage-infected cultures for longer than overnight.

Ladner. *Next, the '484 patent also teaches incubation times greater than 4 hours. The relevant passage in the '484 patent is at col. 144, lines 17-35. As stated therein:*

> We added 1.1 . 10^8 plaque forming units of the KLMUT library to 10 µl of a 50% slurry of agarose-immobilized human neutrophil elastase beads (HNE from Calbiochem cross-linked to Reacti-Gel™ agarose beads from Pierce Chemical Co. following manufacturers directions) in TBS/BSA. Following 3 hours incubation at room temperature, the beads were washed and phage was eluted as done in the selection of EpiNE phage isolates

> (Example IV). The progression in lowering pH during the elution was: pH 7.0, 6.0, 5.0, .4.5, 4.0, 3.5, 3.0, 2.5, and 2.0. **Beads carrying phage remaining after pH 2.0 elution were used to infect XL1-Blue™ cells that were plated to allow plaque formation.** The 348 resulting plaques were pooled to form a phage population for further affinity selection. A population of phage particles containing $6.0 \cdot 10^8$ plaque forming units was added to 10 μl of a 50% slurry of agarose-immobilized HNE beads in TBS/BSA and the above selection procedure was repeated. (emphasis added)

The '484 patent teaches that phage-infected XL1-Blue™ cells are plated to allow plaque formation. For the type of phage used in these experiments, in the plated XL1-Blue™ cells, plaque formation takes longer than 4 hours to occur. Indeed, even under favorable growing temperatures (e.g., 37°C), plaque formation typically occurs after ***about 12-18 hours****. Thus, in view of the '484 patent, a skilled practitioner would understand that phage-infected cells would need to be incubated for longer than 4 hours.*

Anderson. *The disclosure in the '419 patent is limited with regard to methods involving phage. For example, as stated at col. 23, line 65 to col. 24, line 8:*

> The protein-coated beads are also used for determining and/or purifying a receptor from a combinatorial library of compounds or receptor display microorganisms or cells. As such, the beads provide a solid phase substrate for separation. Of particular concern are antibody display phage libraries constructed from immunoglobulin sequences obtained from naive animals or from animals that have been immunized to the protein or a mixture of proteins. The phage which bind to the beads may be later eluted and cultured to produce large quantities of protein binding receptor.

Anderson fails to describe or suggest any time period for incubating phage-infected cells.

Thus, in my opinion, in light of this combination of references, it would not have been obvious to perform the step of producing or amplifying phage in less than 4 hours, as recited in the claims. The references teach that much longer incubation times are needed.

The Declaration goes on to describe why the advantages provided by the claimed methods are significant (see, e.g., item 6). In part, item 6 of the Declaration states:

6. In my opinion, the advantages provided by the methods recited in the amended claims are significant. For example, as described in the application, using methods known in the art, a single round *of selection takes* one to five days *to complete (see, e.g., par. bridging pages 1-2). As a result, if multiple rounds of selection are performed, the process would take well over a week. In large part, this is because such methods require that after selection against a target, phage that bind to the target are used to infect host cells and the phage-infected cells are grown for long periods of time, typically overnight. After the overnight growth, the phage must be*

pooled and/or purified before being used for another round of selection. Pooling and/or purifying steps further lengthen the total time needed to complete the selection procedure.

In contrast, the claimed methods allow for multiple rounds of selection to be completed in a single day (see, e.g., page 15, first full par.) …

The Declaration (e.g., at item 9) summarizes its position and indicates that the claimed methods could not have been arrived at by routine experimentation. As stated therein:

9. Summary: In my opinion, the significant advantages afforded by the claimed methods could not have been arrived at by routine experimentation, but instead required inventive thought. As the above-quoted passages from the '681 patent, the '484 patent, and the '419 patent make clear, traditional methods of selection require laborious and time-consuming steps that are minimized or avoided by the present methods.

For example, in the '681 patent, phage that bound to target were eluted. Then the eluted phage were used to infect bacterial cells, and the cultures were incubated for longer than overnight. The next day, the phage had to be prepared from the overnight cultures and then another round of selection with fresh target could be initiated.

In the '484 patent, phage that bound to target were used to infect bacterial cells, the phage-infected bacterial cells were incubated until plaques formed. The plaques had to be pooled, and then another round of selection with fresh target could be initiated.

The '419 patent provides more limited teachings, fails to describe or suggest any time for incubating phage-infected cells, and indicates that any phage that bind to target have to be eluted. The '419 patent merely discloses that the phage must then be cultured to produce "large quantities."

In contrast, the claimed methods minimize or avoid such steps. For example:

- the claimed methods do not require long (e.g., overnight) periods of incubation after bacteria are infected with target-specific phage;

- the claimed methods do not require preparation or pooling of phage from the bacterial cells;

- the methods do not require large quantities of phage to be produced.

Indeed, Applicants have discovered, inter alia, *that target-specific phage can be used to infect bacteria, even when in the presence of target. No elution step is required. Further, no*

phage preparation or pooling step is needed after phage-infected bacteria are cultured. Of particular significance, Applicants have discovered that large quantities of phage from a given round of selection do not need to be prepared prior to initiating a subsequent round of selection. As a result, dramatically reduced incubation times can be employed after bacteria are infected with phage. Indeed, not only can the cultures be incubated for less than 4 hours, but even times of less than 2 hours or 1 hour can be sufficient. In my opinion, methods with these advantages could not have been easily arrived at using routine experimentation.

Applicants submit that, for at least these reasons, claims 1, 20, and 24 (and their rejected dependencies) are non-obvious over the combinations of cited references. Further, the '108 patent and the '729 patent fail to remedy the deficiencies of the '484 patent; the '419 patent; and the '681 patent.

Withdrawal of these rejections is respectfully requested.

CONCLUSION

Applicants respectfully submit that all of the pending claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

A Request for Continued Examination is being filed herewith.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,
Ladner et al., *Applicants*

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Docket No.: D2033-701910/ 10280-053001
Date: September 22, 2009
961397.1